Lung Cancer Relationships in Women

Lung cancer death rates for women are presently much lower than the corresponding rates for men. In addition, it has been observed that among certain strains of mice exposed to carcinogenic agents, the male animals show a greater tendency to develop lung tumors than do the females (*200, 307*) although there are strains for which this is apparently not so. The extent of the influence of endocrine factors in the sex variation in the incidence of lung tumors is unknown.

As of 1967 in the United States, women accounted for only about one-sixth of the total deaths from lung cancer (*289*). However, the lung cancer death rate in women has risen by over 400 percent in the past 40 years. From 1950 to 1967 alone, the rate per 100,000 population doubled, increasing from 4.5 to 8.9 (*289, 290*).

A number of retrospective studies concerning lung cancer and cigarette smoking among women have found that the difference in the prevalence of lung cancer between males and females is accounted for principally by those tumors classified as Kreyberg's Group I (*154, 311*). These, as was noted above, are the tumors, particularly in males, which show the closest relationship with smoking. Haenszel, et al. (*113*), in a study of 158 women with lung cancer, observed that the sex differential for lung cancer death rates diminishes, but does not fully disappear when only nonsmokers are considered.

Hammond (*118*) found that the death rate for lung cancer in nonsmoking males was somewhat higher than for nonsmoking females. However, the difference in male-female rates was much greater when smokers were compared. It appears that a substantial part of the difference in death rates between male smokers and female smokers can be explained mainly by differences in their smoking habits.

These differences in smoking habits between males and females are of two types. First, overall consumption among females is still significantly lower than that among males. In 1966 (*281*), 30 percent of males reported that they had never smoked while for females the corresponding figure was 59 percent. This study also noted that nearly three times as many males as females reported consuming more than 20 cigarettes per day. Second, it has been shown that women smoke differently than men (*303*) : They begin smoking later than men (*114*) and do not smoke cigarettes as close to the end, where proportionally more nicotine and "tar" are inhaled. Women smoke more filter-tip and "low tar and nicotine" cigarettes than men. Furthermore, cigarette smoking still tends to be heavily concentrated among women under the age at which lung cancer is most likely to occur.

Finally, analysis of the ratio of male and female lung cancer death rates (*283, 284, 285, 286, 287, 288, 289, 290*) reveals that since 1960 this ratio has shown a steady decline, reflecting the greater relative rise in mortality from lung cancer in the female population.

LUNG CANCER, THE URBAN FACTOR, AND AIR POLLUTION

A number of studies have been concerned with the relative influences of smoking, urban residence, and air pollution in the etiology of lung cancer. Table 9 lists studies performed in the United States, Great Britain, and Japan which have dealt with this question. Kotin and Falk (*149, 150*) and more recently the Royal College of Physicians (*228*) have reviewed the literature concerning the influence of atmospheric and environmental factors in the pathogenesis of lung cancer.

The studies listed in table 9 show a number of important trends. Lung cancer death rates are found to be higher among urban populations than among rural populations. It is not known to what extent this urban factor in the etiology of lung cancer is due to differences in the levels of air pollution. Other factors associated with urban residence which may influence the etiology of lung cancer are: differences in smoking habits between the two populations, occupational differences, and possible differences in the reporting of lung cancer deaths (*228*).

The studies also uniformly show that within each urban/rural grouping, lung cancer death rates increase with increased smoking. Whether air pollution acts with cigarette smoking to influence lung cancer death rates in a combined manner is presently unclear (*112, 126, 264, 265*), and the evidence concerning a separate role of air pollution in the etiology of lung cancer is still inconclusive (*228*).

The recent report of the Royal College of Physicians on air pollution and health (*228*) concluded that "the study of time trends in the death rates of lung cancer in urban areas demonstrates the overwhelming effect of cigarette smoking on the distribution of the disease. Indeed, only the detailed surveys that have taken individual smoking histories into account have succeeded in separating the relatively very small influence of the 'urban factor' on the overriding effect of cigarette smoking in the development of cancer of the lung."

TABLE 9.—*Epidemiologic investigations concerning the relationship of lung cancer to smoking, air pollution, and urban or rural residence*

(Actual number of deaths shown in parentheses)

Author, year, Country, reference	Population studied and method of data collection	Results								Comments
		Lung cancer mortality (1950) per 1,000								
			Males			*Females*			*Nonsmokers*	
			London	*Other urban*	*Rural*	*London*	*Other urban*	*Rural*	*All areas*	
Doll, 1953, England (*70*).	Estimated death rates from lung cancer in English population and among nonsmokers obtained from general register.	Age:								Authors noted that estimates are based on very few deaths.
		25–44	0.126	0.095	0.070	0.028	0.028	0.012	0.020	
		45–64	1.572	1.264	0.851	0.194	0.152	0.120	0.090	
		65–74	3.124	2.006	1.164	0.440	0.326	0.288	0.219	

Author, year, Country, reference	Population studied and method of data collection	Results				Comments
		Male lung cancer death rates 1952–54 (per 100,000) ages 54–74				
			Rural (68)	*Mixed (118)*	*Urban (539)*	
Stocks and Campbell, 1955, England (*265*).	Death rates in England and Northern Wales. Review of patient chart or interview with kin or physicians.	Nonsmokers	14	..	131	The authors noted the upward gradient among nonsmokers, pipe smokers and light cigarette smokers and the lack of a similar gradient among moderate and heavy cigarette smokers.
		Pipe	41	25	143	
		Cigarettes: Light	87	153	297	
		Moderate	183	132	287	
		Heavy	363	303	394	

Author, year, Country, reference	Population studied and method of data collection	Results					Comments
		Age standardized death rates due to bronchogenic carcinoma (males)					
			Rural	*Suburb or town*	*City of 10,000–50,000*	*City of >50,000*	
Hammond and Horn, 1958, U.S.A. (*120*).	187,783 white males in 9 states. Questionnaire and interview.	Nonsmokers	...	4.7 (2)	9.3 (3)	14.7 (4)	Data excluded adenocarcinoma. when standardized for age and smoking, rural rate was still noted to be 25 percent less than urban.
		Cigarette smokers	65.2 (52)	71.7 (67)	70.9 (59)	85.2 (83)	

TABLE 9.—*Epidemiologic investigations concerning the relationship of lung cancer to smoking, air pollution, and urban or rural residence (cont.)*

(Actual number of deaths shown in parentheses)

Author, year, Country, reference	Population studied and method of data collection	Results	Comments
Haenszel et al., 1962, U.S.A. (*112*).	10 percent of all white male lung cancer deaths in U.S.A. for 1958 for whom next of kin or physicians supplied smoking data. 2,191 cases with adequate information.	*Age- and smoking-standardized lung cancer mortality ratios (epidermoid and undifferentiated carcinomas only)* *Metropolitan counties* >50,000 ....119 10,000–50,000 ....151 2,500–10,000 ....99 *Nonmetropolitan counties* 2,500–50,000 ......90 Rural nonfarm ....74 Farm 57	Standardized Mortality Ratio = 100 for U.S. white males age 35 and over in 1958. The authors also noted "... joint effects of residence and smoking histories in the schedule of lung-cancer rates far greater than those expected on the assumption of additivity of the separate effects ..."
Doll and Hill, 1964, England (*74*).	41,000 male British physicians. Questionnaire and follow-up of death certificate.	*Standardized death rates for lung cancer* (see below)	The authors noted that rural mortality data were affected by a significant number of city residents retiring to the country.
Wicken, 1966, Northern Ireland (*308*).	1,908 male and female lung cancer deaths over 35 years of age from register. Personal interviews with kin or physicians.	*Lung cancer death rate per 100,000—age- and smoking-standardized* (see below)	Total number of deaths noted under method of data collection include 954 controls.

Doll and Hill, 1964 — *Standardized death rates for lung cancer*

	Conurbation (49)	*Large Towns (34)*	*Small Towns (32)*	*Rural (18)*
Nonsmokers	0.03	0.00	0.11	0.12
Cigarette smokers:				
1–14	0.48	0.32	0.87	0.52
15–24	1.31	1.88	1.06	1.15
>25	1.90	4.43	2.20	1.17

Wicken, 1966 — *Lung cancer death rate per 100,000—age- and smoking-standardized*

	Inner Belfast	*Outer Belfast*	*Belfast Environs*	*Urban Areas*	*Small Towns*	*Rural*
Males	157 (241)	139 (157)	135 (45)	118 (185)	137 (26)	47 (149)
Females	22 (38)	17 (24)	12 (6)	23 (35)	22 (5)	12 (43)

TABLE 9.—*Epidemiologic investigations concerning the relationship of lung cancer to smoking, air pollution, and urban or rural residence (cont.)*

(Actual number of deaths shown in parentheses)

Author, year, Country, reference	Population studied and method of data collection	Results							Comments
Buell et al., 1967, U.S.A. (*49*).	304 lung cancer deaths among American Legionnaires aged 25 and over. Questionnaires to next of kin.	*Age-adjusted lung cancer death rates per 100,000 man years and mortality ratios*							The authors noted the lack of death-rate difference between Los Angeles and San Francisco regions and concluded that photochemical smog is not related to lung cancer.
			Los Angeles		*San Francisco/ San Diego*		*All other California counties*		
			Rate	*Ratio*	*Rate*	*Ratio*	*Rate*	*Ratio*	
		Nonsmokers	28.1	2.5	43.9	3.9	11.2	1.0	
		Smokers:							
		<1 pack/day	63.6	5.7	77.1	6.9	61.02	5.4	
		±1	126.0	11.3	134.5	12.0	124.9	11.2	
		>1	241.3	21.5	226.0	20.2	137.5	12.3	

Author, year, Country, reference	Population studied and method of data collection	Results				Comments
Hitosugi, 1968, Japan (*126*).	185 male and female lung cancer deaths and 4,191 matched controls aged 35–74. Data from questionnaires and interviews.		*Lung cancer death rate per 100,000*			The authors postulated a slight synergistic effect between smoking and air pollution.
			Pollution region			
		Males	*Low*	*Intermediate*	*High*	
		Nonsmokers	11.5	3.8	4.9	
		Smokers:				
		1–14 cigarettes/day	10.6	14.2	23.5	
		>15	21.3	18.6	31.4	
		Females				
		Nonsmokers	4.6	6.9	3.8	
		Smokers:				
		1–14 cigarettes/day	19.7	16.5	15.3	
		>15	12.4	20.5	17.1	
			Age- and smoking-adjusted lung cancer death rate per 100,000			
			Low	*Intermediate*	*High*	
		Males	16.1	22.4	28.4	
		Females	7.5	11.6	8.7	

Uranium Mining

The excess risk for the development of lung cancer among uranium and fluorspar miners has been known for more than 30 years. In a recent review, Bair (*17*) noted that radon and radon-decay products are the only inhaled radionuclides to be epidemiologically related to lung cancer. Lundin, et al. (*178*), in a continuation of the work initiated by Wagoner, et al. (*299, 300, 301*), have recently reported on a 17-year follow-up of 3,414 white underground uranium miners. The authors estimated that smoking uranium miners experienced an excess of lung cancer ten times greater than did nonsmoking miners.

Saccomanno (*231*), in recent testimony, analyzed the data of the United States Public Health Service (USPHS) Study Group as presented by Lundin, et al. (*178*) above. He reported that cigarette smoking uranium miners incurred lung cancer rates four times greater than those of other cigarette smokers.

Of the 62 lung cancer deaths in this population, 60 occurred in smokers. He also observed that among 100,000 uranium miners 700 lung cancer deaths per year would be expected to occur among cigarette smokers compared with only 4 among nonsmokers.

Other Occupations

Nelson (*199*) has recently reviewed certain environmental and occupational hazards as they relate to inhalation carcinogenesis. He observed that cancer of the respiratory tract has been linked epidemiologically and, in some cases, experimentally with occupational exposure to the following materials: chromium, nickel, arsenic, and asbestos. Doll (*72*) and Goldblatt (*100*), in earlier reviews, also noted an association with coal, natural gas, and graphite exposures.

Nickel

Morgan (*194*) noted that much of the nasal and lung cancer attributed to nickel exposure may have been due to arsenical impurities found in processed nickel prior to 1925. Doll (*69*) found that the number of excess deaths among nickel workers under 50 years of age had declined following the change in nickel manufacturing processes. The experiments of Hueper (*134*) and Sunderman, et al. (*267, 268, 269*) have shown that both guinea pigs and rats develop lung cancer following chronic exposure to nickel carbonyl or nickel dust. Sunderman and Sunderman (*270*) also reported that cigarette smoke contains nickel and that this concentration of nickel may be capable of inhibiting the induction of lung aryl hydroxylase, an enzyme which is able to detoxify aromatic hydrocarbons including known carcinogens such as benzo[a]pyrene.

Asbestos

In 1955, Doll (*71*) found that lung cancer was a definite hazard among asbestos workers. In a more recent study, Selikoff, et al. (*251, 252*) examined the relationship of smoking and asbestos exposure to lung cancer. These authors followed 370 people who had been asbestos workers during the years 1942–1962. Over a 5-year follow-up period, 94 deaths occurred in this group, of which 24 were due to bronchogenic carcinoma. The authors noted that according to data obtained from Hammond (*118*), only 3.16 deaths from lung cancer would have been expected among smokers, and calculated a 7.6 to 1.00 mortality ratio due to asbestos exposure. None of the 87 nonsmokers or pipe and cigar smokers died of lung cancer. When the expected number of nonsmoker deaths (0.26) is compared with the actual number (*24*) which occurred among the smoking asbestos workers, an extremely high mortality ratio of 92 to 1 is obtained, thus reflecting the possible interaction of asbestos exposure and cigarette smoking.

Exposure of mice (*179*) and rats (*106*) to asbestos dust or the intratracheal injection of chrysotile asbestos dust has resulted in the production of significant numbers of primary pulmonary carcinomas. Miller, et al, (*184*) exposed hamsters to intractracheal injections of benzo[a]pyrene. These authors observed that the addition of the chrysotile variety of asbestos to the injections appeared to promote benzo[a]pyrene carcinogenesis in the respiratory tract, as determined by the time of appearance and yields of papillomas and carcinomas.

Arsenic

A recent epidemiologic study by Lee and Fraumeni (*163*) has indicated an excess of lung cancer deaths among smelter workers exposed to arsenic for more than one year. Cigarette smoking was not taken into account in their computations. Experimental work on the induction of cancer in animals using arsenic has yielded either negative or inconclusive results (*133, 135*).

Chromium

Exposure to industrial bichromate compounds has been associated with an excess of lung cancer deaths (*22,255*). Laskin, et al. (*159*) have recently reported that intrabronchial pellet implantation of various chromium compounds in rats is associated with the development of squamous cell carcinomas and adenocarcinomas. However, Nettesheim, et al. (*200*) exposed mice to chromium oxide dust and observed that it had no discernible effect on lung tumor incidence.

Pathological Studies

Investigators who have conducted detailed autopsy studies on patients who died of lung cancer have reported the increased presence, when compared to noncancer patients, of bronchial epithelial changes which they considered to be precursors of bronchogenic carcinoma (*7, 8, 23, 51, 104, 208, 220, 279, 309*). Such changes include squamous metaplasia, atypical squamous metaplasia (with acanthosis, dyskeratosis, and numerous mitotic figures), and carcinoma *in situ*. Carnes (*51*) noted that carcinoma *in situ* was present in 119 cases of lung cancer but not in any of the 119 controls who were matched for age, sex, and race.

Autopsy studies comparing the frequency of these cancer-related changes in the lungs of smokers and nonsmokers are presented in table 10. Virtually all the studies noted an increased prevalence of these epithelial alterations among smokers as compared with nonsmokers. Definite dosage-dependent relationships were evident in the results of many of the reports. Also, Auerbach, et al. (*14*) observed that the number of cells with atypical nuclei decreases progressively in the bronchial mucosa of ex-cigarette smokers, depending upon the number of years between cessation of smoking and death, although it usually remains above that found in nonsmokers.

The cytologic studies included in this table (*182, 198, 222*) all noted an increased percentage of sputum specimens showing metaplasia among smokers as compared with nonsmokers.

Pulmonary Carcinogenesis

General Aspects of Carcinogenesis

Agents found in cigarette smoke which have been identified as, or are suspected of being carcinogenic, are listed in table 11. The list includes certain compounds which most probably contribute to the pathogenesis of the various cancers discussed in the other sections of this chapter. Many other agents have been identified in tobacco and tobacco smoke. At the present time, they do not appear to bear a direct relationship to carcinogenesis. Stedman (*262*) and Wynder and Hoffmann (*319*) provide detailed listings and discussions concerning these materials.

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results						Comments
Chang, 1957, U.S.A. and Korea (*55*).	105 males and females 40–86 years of age.		*Percent of cases with bronchial basal cell hyperactivity*					Smokers included pipe and cigar smokers. † p≦0.01 in comparison with nonsmokers.
		Nonsmokers	23.5 (34)					
		Smokers	43.7 (71)					
		Heavy smokers	†61.3 (31)					
Hamilton et al., 1957, U.S.A. (*117*).	Selected autopsy material.		*Number*	*Age range*	*Percent of cases with:* *Basal cell hyperplasia*	*Squamous metaplasia*	*Transitional metaplasia*	No lung cancer patients included.
		Smokers	15	39–77	86.6	20.0	40.0	
		Nonsmokers	20	28–83	40.0	15.0	35.0	
Sanderud, 1958, Norway (*240*).	100 males autopsied at Gade Institute on whom smoking data was available.		*Percent of cases with bronchial squamous epithelial metaplasia*					Nonsmokers include those smoking less than or equal to 5 grams per day.
		Nonsmokers	54.0 (39)					
		Pipe	80.5 (20)					
		All cigarette	79.0 (38)					
		Cigarettes per day:						
		5–14	70.0 (23)					
		15–25	90.0 (10)					
		>25	100.0 (5)					
Knudtson, 1960, U.S.A. (*147*).	100 persons 23–85 years of age autopsied at Seattle Veterans Hospital on whom smoking data was available.		*No. of Persons*	*Percent of cases with:* *No change*	*Basal cell hyperplasia*	*Squamous metaplasia*	*Atypical proliferative metaplasia*	Age, occupation, and site of residence were found to have no appreciable effect.
		Nonsmokers	(21)	47.6	28.6	14.3	9.5	
		Cigarettes/day:						
		1–9	(9)	77.8	11.1	11.1	..	
		10–15	(11)	18.2	18.2	54.5	9.1	
		16–20	(44)	20.4	29.5	29.5	29.5	
		>21	(9)	11.1	33.3	44.4	11.1	
		Pipe or cigar	(6)	..	100.0	..	..	

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers (cont.)*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results	*Number of persons*	*Number of sections of bronchial epithelium*	*Percent sections with cilia absent and entirely atypical cells*	*Percent sections with some atypical cells and cilia absent*	Comments
Auerbach et al., 1961, U.S.A. (*12*).	339 persons 22–88 years of age autopsied at East Orange Veterans Hospital (excludes lung cancer).	Nonsmokers:					The authors noted a dose-response relation of smoking to: a. loss of cilia, b. increase in number of atypical cells, c. carcinoma *in situ*. Average number of sections per case equaled 52.3.
		<40 years of age	8	383	..	0.3	
		40–59	11	560	..	..	
		60–69	28	1,463	..	0.1	
		>70	18	918	..	0.5	
		Smokers <1 pack/day:					
		<40 years of age	14	727	0.1	4.7	
		40–59	24	1,240	1.0	16.9	
		60–69	35	1,772	0.5	10.8	
		>70	22	1,101	0.6	9.4	
		Smokers >1 pack/day:					
		<40 years of age	17	880	1.5	12.5	
		40–59	63	3,027	4.5	17.4	
		60–69	84	4,186	6.9	20.5	
		>70	15	756	9.8	23.7	

Author, year, country, reference	Number of cases and method of selection	*Percent sections showing changes in bronchial epithelium (number of sections)*	*Normal*	*Hyperplasia*	*Squamous metaplasia*	*Atypical metaplasia*	*Carcinoma in situ*	*Carcinoma*	Comments
Cross et al., 1961, U.S.A. (*64*).	140 persons autopsied at Iowa City Veterans Hospital on whom smoking data was available.	Nonsmokers (31)	61(562)	36(137)	8 (33)	†15 (58)	....	....	† The authors noted that the difference between smokers and nonsmokers was statistically significant.
		Smokers (109)	44(570)	43(562)	16(197)	20(263)	1(12)	2.6(34)	

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers (cont.)*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results						Comments
Auerbach et al., 1962, U.S.A. (*14*).	72 autopsied former cigarette smokers who had been smoking for ≧10 years and had ceased ≧5 years ago.		*Number*	*Number of sections of bronchial epithelium*	*Percent sections with cilia absent and entirely atypical cells*	*Percent sections with some atypical cells and cilia absent*	*Percent sections with 50 percent atypical cells and cilia present*	Each ex-smoker matched with a current smoker plus never-smoker for age, occupation, and residence. There was an average of 50.3 sections per subject and none had less than 18 sections.
		Nonsmokers	72	3,156	0.0	0.1	0.5	
		Ex-smokers	72	3,436	0.2	0.9	2.5	
		Current smokers	72	3,537	8.0	19.0	80.8	

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers (cont.)*

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results						Comments
			Number	*Number of sections of bronchial epithelium*	*Percent sections with cilia absent and entirely atypical cells*	*Percent sections with some atypical cells and cilia absent*	*Percent sections with 50 percent atypical cells and cilia present*	
Auerbach et al., 1962, U.S.A. (*13*).	456 male and 302 female smokers and nonsmokers autopsied and matched for age, occupation, and residence.	Males:						Major findings noted: Urban nonsmokers showed more lesion than rural. Both lesions and atypical nuclei were much less frequent in nonsmokers and less frequent in pipe and cigar smokers than in cigarette smokers. 57.1% of cases had 50–55 sections 31.5% of cases had 40–49 sections 7.3% of cases had 30–39 sections 4.6% of cases had 16–29 sections
		Nonsmokers	47	2,346	..	0.1	0.7	
		Cigarette smokers	75	3,393	6.9	21.2	78.5	
		Females:						
		Nonsmokers	47	2,379	..	0.1	0.5	
		Cigarette smokers	75	3,507	2.5	13.3	62.6	
		Males:						
		Nonsmokers	35	1,706	..	0.2	0.5	
		Cigar smokers	35	1,733	0.3	10.0	10.7	
		Cigarette smokers	35	1,526	12.8	27.3	83.1	

Author, year, country, reference	Number of cases and method of selection	Results	*Percent in each cytologic class*				Comments
			Normal	*Slightly atypical*	*Moderately atypical*	*Strongly atypical*	
Robbins, 1966, U.S.A. (*222*).	103 students 17–24 years of age who underwent aerosol sputum induction.	Nonsmokers (45)	86.7	4.4	8.9	..	Smokers defined as those having consumed ≧10 cigarettes a day for ≧1 year.
		Smokers (58)	55.2	32.8	10.3	1.7	

TABLE 10.—*Pathologic and cytologic findings in the tracheo-bronchial tree of smokers and nonsmokers* (*cont.*)

(Actual number of cases shown in parentheses)

Author, year, country, reference	Number of cases and method of selection	Results						Comments
Maltoni et al., 1968, Italy (*182*).	1,000 healthy males who underwent sputum induction.		*Number*	*Percent showing metaplasia*				
		Nonsmokers	294	41.16				
		Smokers:						
		1–10 cigarettes/day	189	47.09				
		11–20	385	51.43				
		21–30	93	61.29				
		>30	39	69.23				
Nasiell, 1968, Sweden (*198*).	50 nonsmoking outpatients, 398 smokers participating in general health examination who underwent sputum induction.	*Sputum cytologic changes*	*Number*	*Percent Males*	*Mean age*	*Percent with metaplasia*	*Percent with atypical metaplasia*†	† Regarded by author as "real premalignant change."
		Nonsmokers	50	42	57.1	18	4	
		Smokers	398	73	45.6	62	27	
Spain et al., 1970, U.S.A. (*258*).	157 males and 78 females autopsied following sudden or accidental death for whom smoking data were available (ex-smokers excluded from female data).		*Number*	*Percent with metaplasia*				The authors found no evidence of carcinoma *in situ* or preneoplastic atypical changes.
		Males:	-					
		Nonsmokers	36	50.0				
		Ex-smokers	21	57.7				
		<1 pack	32	62.5				
		>1 pack	68	73.5				
		Females:						
		Nonsmokers	34	34.1				
		<1 pack	18	33.3				
		>1 pack	26	46.1				

In order to facilitate understanding of the relationships of the various compounds to one another, the third column presents the presently understood relative importance of each of the various groups of compounds. These compounds have been tested only in animals or tissue cultures, and it should be stressed that the relative importance of one compound may not be the same in man as it is in animals.

Table 11 is divided into two major sections. The first section details those compounds which are considered to be or are suspected of being cancer initiators. These are compounds which induce irreversible changes in responsive cells. In the second section are listed those compounds which are considered to be or are suspected of being tumor promoters. These compounds promote the malignant reproduction of cells in which neoplastic changes have been initiated. A number of these initiators may also act as complete carcinogens in their own right. The evidence concerning the two stage initiation-promotion mechanism is still rather limited for respiratory tract carcinogenesis.

The *polynuclear aromatic hydrocarbons* (PAH) listed are presently considered to play a very significant role in pulmonary carcinogenesis due to tobacco smoking. These compounds act as tumor initiators or complete carcinogens. The particular role of these agents in environmental and occupational carcinogenesis has been reviewed by Falk, et al. (*93*). That such hydrocarbons are produced from tobacco during human smoking has been shown by Kiryu and Kuratsune (*146*). These authors reported the presence of benz[a]anthracene, chrysene, benzo[a]pyrene, and benzo[b]fluoranthene in the "tar" produced by normal smoking and measured in either filters or stubs.

Two hydrocarbons which have frequently appeared in the literature on experimental tobacco carcinogenesis may not actually be present in tobacco smoke. They have been used as representatives of carcinogenic PAH, a class which includes many constituents that have been identified in cigarette smoke condensate. They are 7,12-dimethylbenz[a]anthracene and 3-methylcholanthrene and have been frequently used as tumor initiators or complete carcinogens, particularly in skin painting and tracheal implantation experiments.

The *nitrosamine compounds* listed are potent carcinogens affecting many organ systems, including the respiratory tract (*188, 189*). Magee and Barnes (*181*) have presented a detailed account of experiments in this area. Nitrosamines have been identified in trace amounts in tobacco "tar" and the conditions required for their formation (the presence of secondary amines and nitric oxide) are

TABLE 11.—*Identified or suspected tumorigenic agents in cigarette smoke*[1]

Components	Estimated concentration in 100 cigarettes (85 mm. nonfilter)	Presently understood relative importance in experimental tobacco carcinogenesis
I. Complete carcinogens and tumor initiators:		
Polynuclear aromatic hydrocarbons	10-30 ug	Tumor initiators.
1. Benzo(a)pyrene	3.9	
2. Dibenz(a,h)anthracene	0.4	
3. Benzo(b)fluoranthene	0.3	
4. Benzo(j)fluoranthene	0.6	
5. Dibenzo(a,i)pyrene	Trace	
6. Benz(a)anthracene	0.3	
7. Chrysene	2.0	
8. Indeno(1,2,3-cd)pyrene	0.5	
9. Benzo(c)phenanthrene[2]	Trace	
10. Methylbenzo(a)pyrenes	0.1	
11. Methylchrysenes	2.0	
N-heterocyclic hydrocarbons	1-2	Tumor initiators.
1. Dibenz(a,h)acridine	0.01	
2. Dibenz(a,j)acridine	1.0	
3. 7H-dibenzo(c,g)carbazole	0.07	
N-nitrosamines[3]	1-10	Suspected carcinogens of possible importance (presence in fresh smoke possible).
1. Dimethylnitrosamine	0.4	
2. Diethylnitrosamine	Trace	
3. Methyl-n-butylnitrosamine	Trace	
4. Nitrosopyrrolidine	0.4	
5. Nitrosopiperidine	Trace	
Epoxides, peroxy compounds, and lactones:		
1. Epoxides	No data	Certain of these compounds are known carcinogens; presence in smoke condensate not established.
2. Peroxides	Present	
3. Lactones	....	
a. α-Levantenolide	20.0	
b. β-Levantenolide	2.0	
N-alkyl-heterocyclics:		
1. I-methylindole	Present	Possible initiator.
Pesticides and fungicides:[4]		No essential contribution suspected.
1. TDE	10-100	
2. o,p'-DDD	10-100	
3. DDT	10-100	
4. Maleic hydrazide	10-100	
Beta-naphthylamine	2-3	Suspected bladder carcinogen; of doubtful significance at reported levels.
Polonium 210	1-50 picocuries	Of some importance only in the case of relatively high concentration, but not important at reported levels.
Nickel compounds	Present	Suspected carcinogens of some importance.

TABLE 11.—*Identified or suspected tumorigenic agents in cigarette smoke*[1] *(cont.)*

Components	Estimated concentration in 100 cigarettes (85 mm. nonfilter)	Presently understood relative importance in experimental tobacco carcinogenesis
II. Tumor promoting agents:		
Neutral promoters (polymers) (unknown structures.)	No data	Of possible importance.
Volatile phenols	20-30 mg.	Of possible importance.
1. Phenol		
2. Cresol		
Nonvolatile fatty acids	20-100 mg.	Of minor importance.
1. Stearic acid		
2. Oleic acid		
N-alkyl heterocyclics:		Of possible importance.
1. 9-methylcarbazole	Present	

[1] Modified and expanded from (*319, 320*) with reference to (*52, 60, 89, 111, 129, 202, 262, 293, 294, 295*).
[2] Has not been tested as an initiator, but is a known complete carcinogen.
[3] See Neurath, (*202*).
[4] See (*111, 128*).

found in tobacco smoke (*38*). However, nitrosamines may be artifacts dependent on the method of smoke collection (*201*).

Neurath (*202*) considers the nitrosamines listed in table 11 as being present in fresh cigarette smoke (*253, 254*). However, conclusive confirmation of their presence in fresh smoke is not available (*38, 138, 155, 319*).

Certain of the *pesticides* and *fungicides* presently in use on tobacco have been found to be carcinogenic (*91, 273, 280*). A number of these, such as DDT, are now being phased out of regular domestic use. The compounds listed have been shown to be present in trace amounts in mainstream tobacco smoke (*111, 128*). A recent, extensive review by Guthrie (*111*) provides more detailed information concerning these agents.

Radioactive isotopes can be found in tobacco and tobacco smoke (*105*). Potassium-40, while present in tobacco leaf, is not transmitted in any substantial amount to mainstream smoke (*230*). Polonium-210 (Po_{210}), however, is transmitted into the mainstream smoke (*94, 123, 142, 145, 215, 217*). A number of autopsy studies (table A12) have shown that the bronchial epithelium of smokers contains significantly more Po_{210} than that of nonsmokers. Little, et al. (*172, 173, 174*) have also noted that the concentration of polonium was markedly higher at sites of bronchial bifurcation. These authors stress the importance of this finding for pulmonary carcinogenesis by noting that bronchogenic carcinomas are frequently located at bifurcations and that the polonium levels which they found in those regions probably have biologic significance (*216*). Other investigators (*123, 217*) have not observed this excess at bifurcations, and in a recent discussion Wynder and Hoffmann (*320*) concluded that it appears unlikely that Po_{210} in the amounts present in cigarette smoke plays a role in tobacco carcinogenesis.

Although not listed as a separate group, there are a number of agents in cigarette smoke which are potent inhibitors of ciliary movement. Their importance in carcinogenesis derives from the increased amount of time which they afford the known carcinogens to be present on the surface of the bronchial epithelium. These inhibitors include volatile aldehydes, hydrogen cyanide, nitrogen oxides, volatile phenols, and certain volatile acids such as formic and acetic (*129*).

Experimental Studies

In some respects, the animal and tissue culture studies detailed below apply to neoplastic transformations, not only in the lung but in other tissues in which tobacco smoke, particularly cigarette smoke, is believed to play a role. These general experiments will be presented here, however, with the experiments which bear on lung tissue directly.

Skin Painting and Subcutaneous Injection

Numerous animal studies on rats, mice, and rabbits, have been performed utilizing known carcinogens, whole tobacco "tar," and various tobacco condensate subfractions, or compounds known to be present in tobacco smoke. These experiments involve the single or repeated painting of shaved or unshaved animal skin. A selected number of these studies is presented in table A13. Numerous other studies, performed prior to and following 1953, are reviewed by Wynder and Hoffmann (*319*).

The skin painting method is still considered to be a valid procedure for the identification of agents suspected of participating in pulmonary carcinogenesis, as well as for the quantification of the reduction in tumorgenicity of specific agents.

Tissue and Organ Culture

The exposure of tissue and organ cultures to cigarette smoke, its condensates, or its constituent compounds has been shown to significantly alter patterns of cell growth and reproduction. Table A14 presents an outline of these experiments. Once again, less severe effects have been noted when filtered smoke was used (*165*).

Tracheobronchial Implantation and Instillation

More complex experiments concerning the carcinogenicity of cigarette and tobacco smoke are represented by those which involve the direct implantation, instillation, or fixation of suspected materials into the tracheobronchial tree of animals. Certain of these experiments are outlined in table A15. Recent reviews by Saffiotti (*233, 234*) Laskin, et al. (*159*), and Montesano, et al. (*189*) as well as that by Wynder and Hoffmann (*319*) provide more detailed and extensive accounts of these experiments.

Of note among the results outlined in this table are the following: The enhanced carcinogenicity found when benzo[a]pyrene (B[a]P) is combined with a carrier such as hematite dust (*235*), and the definite increase in bronchial epithelial preneoplastic and neoplastic changes among dogs treated with smoke condensate as compared with those undergoing only physical bronchial stimulation (*224*).

Inhalation

Various species, including mice, rats, hamsters, and dogs, have been exposed to cigarette smoke or aerosols of its constituents. These inhalation experiments are outlined in table A16. It must be noted that the majority of the studies listed involve the passive inhalation of the material presented usually in a chamber. Active inhalation experiments, exemplified by the work of Rockey and Speer (*223*) and Auerbach and his colleagues (*11, 119*) involved animals which were trained to inhale voluntarily, thus more closely simulating human smoking.

Results of note among these experiments include the following: Mühlbock (*195*) observed that cigarette smoke inhalation enhances the already substantial rate of spontaneous alveolar cell carcinoma formation in hybrid mice, and various investigators induced adenomas in experimental animals (*108, 168, 206*). Harris and Negroni (*121*) found that exposure to cigarette smoke achieved some enhancement of adenocarcinoma formation in mice but did not observe proven squamous cell carcinoma. Some of their mice had also been exposed to Swine influenza virus aerosol. In a related study, Boren (*32*) exposed hamsters to cigarette smoke at set intervals over a 48-hour period. The author observed alterations in pulmonary cell kinetics (the pattern of DNA synthesis) as demonstrated by H^3-thymidine autoradiography. The pattern of the labeling response to cigarette smoke was significantly different from that of the response to high oxygen concentrations.

Auerbach, et al. (*11*) have reported the development of early invasive squamous cell bronchogenic carcinoma in dogs following a period of direct inhalation of cigarette smoke. These investigators trained beagle dogs to inhale cigarette smoke through a tracheostoma (*50*) and divided the animals into groups according to dosage as detailed in table 17. A number of dogs died during the course of the experiment which ran for 875 days, or approximately 29 months. The causes of death are listed in table 18. All of the remaining dogs, with the exception of group "h" (high exposure, heavy weight), were sacrificed shortly after day 875; the survivors among the heavier dogs are continuing to smoke.

Examination of the respiratory tree of the animals revealed a number of tumors (table 19). Most of these were similar to the type of tumor which in man is referred to as bronchiolo-alveolar. This tumor arises in the bronchiolar and alveolar epithelium and tends to be multicentric. Two striking characteristics of these bronchiolo-alveolar tumors were the existence of a histologic spectrum (from a tumor resembling the benign condition of adenosis to frankly malignant tumors with invasion of the pleura and surrounding parenchyma) and the marked tendency to squamous change. Invasive bronchiolo-alveolar tumors were found in 12 dogs in the group which had been exposed to the largest dosage of cigarette smoke. Several had tumors of more than one category. Ten of these dogs had invasive bronchiolo-alveolar tumors which did not extend into the pleura, one dog had an invasive bronchiolo-alveolar tumor which extended to the pleura, and four had invasive bronchiolo-alveolar tumors extending into the pleura beyond the pleural-pulmonary junctions. In addition, two bronchogenic squamous cell carcinomas were found in this group (table 19). The dosage dependence of tumor formation is shown in figures 2 and 3.

Major findings of the study were twofold. First, that smoking filter-tip cigarettes was less harmful, both in terms of pulmonary parenchymal damage and lung tumors, than smoking identical cigarettes without filters. This supports the generally held view that total particulate matter is a meaningful indicator of the carcinogenic potential of a cigarette. Second, lung cancer of two types found in man was produced by the inhalation of cigarette smoke. Two of the dogs were found to have early invasive squamous cell carcinoma of the bronchus, and both belonged to the high-dosage group. These carcinomas were indistinguishable from early invasive squamous cell carcinomas found in the bronchial tubes of human beings who smoke cigarettes. The majority of tumors found in the dogs were of a bronchiolo-alveolar type, which although not as common as squamous cell cancer in man, is not rare in humans. This type is often included in the category of adenocarcinoma. A number of studies have shown an excess of these tumors among

TABLE 17.—*Data on pedigreed male beagle dogs of groups F, L, H, h, and N*

(Some of the figures apply only to dogs surviving 875 days or longer)

	Filter group F	No filter group L	No filter group H	No filter group h	Nonsmokers group N
Number of dogs on day No. 57[1]	12	12	24	38	8
Weight at start (day No. 1) mean weight (pounds)	25.0	25.1	25.0	31.9	30.7
Cigarettes per dog in 875 days	6,143	3,103	6,129	6,129	none
Mean number of cigarettes per day	7.02	3.54	7.0	7.0	—
Equivalent number of cigarettes per day for 150 pound man	42.1	21.2	42.0	32.9	—
Type of cigarettes:[2]					
Milligrams of tar per cigarette	17.8	34.8	34.8	34.8	—
Milligrams of nicotine per cigarette	1.17	1.85	1.85	1.85	—
Total dosage in 875 days:					
Grams of tar per dog	109.3	103.5	207.8	207.8	—
Grams of nicotine per dog	7.19	5.56	11.12	11.12	—
Dosage in 875 days relative to starting weight:					
Grams tar/pounds weight	4.37	4.12	8.31	6.51	—
Grams nicotine/pounds weight	0.29	0.22	0.44	0.35	—

[1] The smoking dogs were divided into groups F, L, H, and h on day No. 57.

[2] Dogs of groups L, H, and h smoked filter-tip cigarettes during a training period at the start of the experiment, but smoked nonfilter cigarettes thereafter.

SOURCE: Adapted from Hammond, E. C. et al. (*119*).

TABLE 18.—*Summary of principal cause of death (days No. 57 through No. 875) in dogs of groups F, L, H, h, and N*

(Each death classified according to most severe condition—some dogs died of a combination of causes listed)

Principal cause of death	Filter tip Group F	No filter Group L	No filter Group H	No filter Group h	Nonsmokers Group N	Total
Pulmonary emphysema and fibrosis	—	—	2	—	—	2
Cor pulmonale (pulmonary emphysema and fibrosis with right heart enlargement)	—	—	3	5	—	8
Pulmonary infarction	1	1	2	5	—	9
Bronchopneumonia	—	—	3	1	—	4
Aspiration of food	1	1	—	....	—	2
Uncertain	—	—	2	1	—	3
Number of deaths	2	2	12	12	—	28
Number surviving 875 days	10	10	12	26	8	66
Total number of dogs	12	12	24	38	8	94

SOURCE: Hammond, E. C. et al. (*119*).

TABLE 19.—*Data on dogs with lung tumors indicating type of tumor and lobe in which the tumor was found*

Group		Day of death	Number of cigarettes	Age at death (years)	Lobes with bronchiolo-alveolar tumors Non-invasive	Invasive	Early squamous cell bronchial carcinoma
Group N (nonsmokers)	N	904a	—	5.1	LA	—	—
	N	904b	—	4.9	RA	—	—
Group F (filter-tip)	F	878a	6,161	5.1	LA	—	—
	F	879a	6,170	4.7	LA	—	—
	F	885a	6,224	5.2	LA	—	—
	F	890a	6,269	5.4	LA	—	—
Group L (no filter)	L	347	1,055	3.8	LA, LC	—	—
	L	812	2,847	5.1	RA	—	—
	L	876a	3,103	5.1	LA, RA	—	—
	L	877a	3,107	5.2	LA, LC	—	—
	L	882a	3,127	5.2	LA, LD	—	—
	L	896a	3,183	5.3	LA, RD	—	—
	L	899a	3,195	5.4	LA	—	—
Group H (no filter)	H	135	518	2.5	RC	—	—
	H	259	1,343	3.3	LA, RA, RD	—	—
	H	563	3,404	4.7	LD, RA	—	—
	H	716	4,689	5.0	..	LA	—
	H	753	5,030	3.8	RI	LA, RA, RD	—
	H	760	5,088	4.2	LA	—	—
	H	858	5,970	5.3	LA	—	—
	H	876a	6,129	4.9	..	LA, LD, RA	—
	H	877a	6,138	5.4	..	LA	LABB
	H	878a	6,147	5.3	RA	LA	—
	H	882a	6,183	5.4	LA	—	—
	H	883a	6,192	4.7	RA, RD, RI	LA	—
	H	885a	6,210	5.0	..	LA, RA	LMB
	H	889a	6,246	5.0	..	LA	—
	H	890a	6,255	4.9	LA	—	—
	H	892a	6,273	5.7	LC, RA	—	—
	H	892b	6,273	5.3	..	LA, RA	—
	H	897a	6,318	5.2	RA	—	—
	H	897b	6,318	4.5	LC	LA	—

TABLE 19.—*Data on dogs with lung tumors indicating type of tumor and lobe in which the tumor was found (cont.)*

Group		Day of death	Number of cigarettes	Age at death (years)	Lobes with bronchiolo-alveolar tumors Non-invasive	Invasive	Early squamous cell bronchial carcinoma
Group h (no filter)	h	606	3,769	4.6	LA	—	—
	h	626	3,928	4.4	..	LA, RI	—
	h	649	4,143	5.0	RI	LA, RA	—
	h	794	5,400	5.1	LA, RA	—	—

LA, left apical lobe; LC, left cardiac; LD left diaphragmatic; RA, right apical; RC, right cardiac; RI, right intermediate; RD, right diaphragmatic; LABB, left apical branch bronchus; LMB, left main bronchus.

For smoking dogs, the day of death indicates the number of days since start of smoking. The letter "a" or "b" follows the day of death of dogs sacrificed after day #875.

SOURCE: Auerbach, O. et al. (*11*).

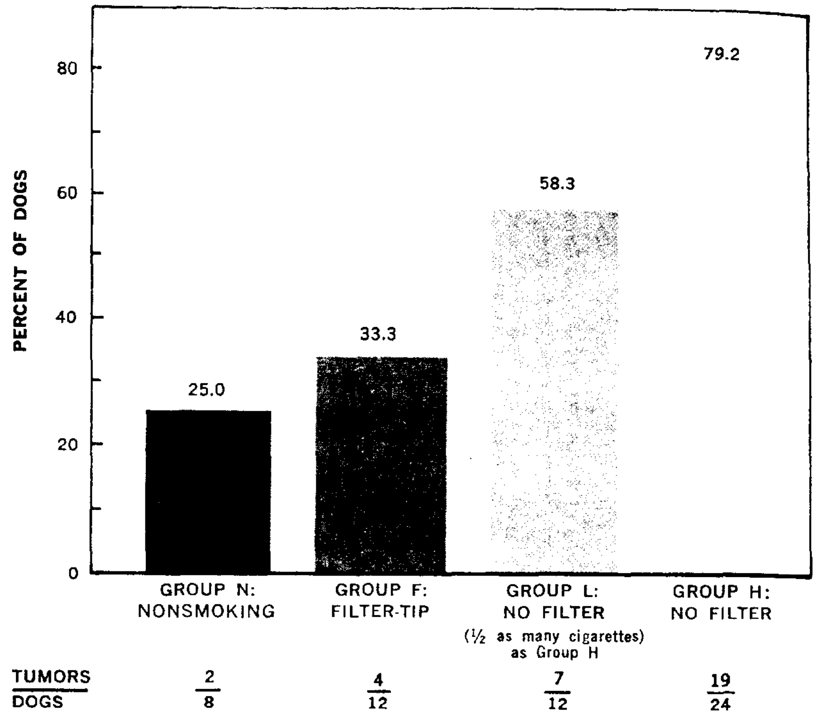

FIGURE 2.—Percent of smoking dogs with tumors.
SOURCE: Adapted from Auerbach, O., et al. (11).

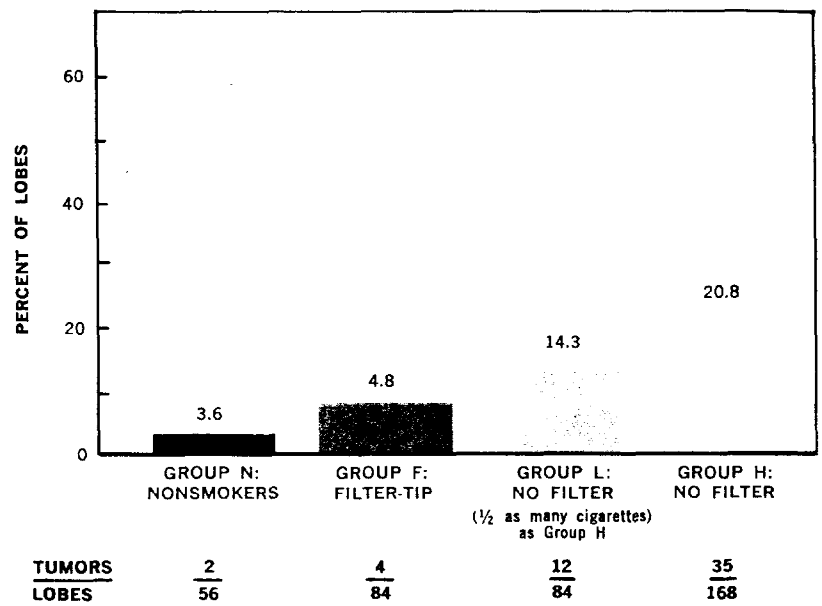

FIGURE 3.—Percent of lung lobes with tumors in smoking dogs.
SOURCE: Adapted from Auerbach, O., et al. (11).

cigarette smokers (*6, 42, 112*), but the magnitude of this relationship is not as great as that with squamous cell cancer in man.

Reduction in Tumorigenicity

The importance of reducing total particulate matter in cigarette smoke is reflected in the dose-dependent results of the Auerbach-Hammond study. A major objective of experimental tobacco carcinogenesis must be the reduction in the tumorigenicity of cigarette smoke and other tobacco products. In a recent article (*320*), Wynder and Hoffmann have reviewed the various methods applied to achieve this goal. Among these methods are the modification of the tobacco itself, the modification of the conditions of tobacco pyrolysis, the use of additives, and the use of filters. The use of filters should produce a reduction of particulate matter as well as of gas phase components.

Bross (*44*) studied 974 cases of lung cancer at Roswell Park Memorial Institute and concluded that smokers who switched to filter cigarettes showed a decreased risk of developing lung cancer. However, even after switching, heavy smokers were still found to have a mortality risk five times that of nonsmokers.

More recently, Wynder, et al. (*324*) reported on an interview study of 350 patients with histologically confirmed lung cancer and 552 age and sex-matched controls. They found that subjects who had switched from nonfilter to filter cigarettes ten or more years prior to the study incurred a lower relative risk of lung cancer at all consumption levels than that incurred by those who continued to smoke nonfilter cigarettes. The authors suggest that this difference in relative risk may be due to the lower "tar" content in filter cigarette smoke. Prospective studies concerning the effects of filter cigarette smoking are presently being conducted.

Apart from variations in "tar" exposure due to filtration, it appears that different patterns of smoking result in the inhalation of varied amounts of "tar." Graham, et al. (*103*) simulated different inhalation patterns with the use of an analytic smoking machine. He found that smoking a given number of puffs over a long period of time results in greater "tar" retrieval than smoking them over a short period. Also, he observed that taking most of the puffs at the end of the cigarette results in the highest retrieval while taking most at the beginning results in the smallest retrieval. Complementing these observations is the same author's case/control study (*102*) of 183 men with lung cancer and 161 men with diseases not related to tobacco smoking. He found that the lung cancer patients had significantly greater high "tar" yield cigarette smoking patterns than the controls. The risk of lung cancer was found to increase with the increase in mean number of puffs per